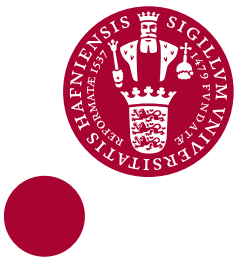

Identification of novel biomolecules and their molecular targets which regulate lipid homeostasis in C. elegans

Olsen, Louise Cathrine Braun; Nielsen, John; Sonne, Si Brask; Kristiansen, Karsten; Færgeman, Nils J.

Published in:
Chemical Biology - Molecules to Probe Life

Publication date:
2009

Document version
Publisher's PDF, also known as Version of record

FUNCTIONAL GENOMICS SYMPOSIUM

CHEMICAL BIOLOGY – MOLECULES TO PROBE LIFE

10th annual conference in Göteborg
August 24-25, 2009
Chalmers Conference Center,
Chalmersplatsen 1

PROGRAMME AND ABSTRACT BOOK

Center for Chemical Biology
University of Gothenburg

Gothenburg Center for
Systems Biology

UNIVERSITY OF GOTHENBURG

CHALMERS

P6

Identification of novel biomolecules and their molecular targets which regulate lipid homeostasis in *C. elegans*.

Louise C. B. Olsen[1], John Nielsen[2], Si Brask Sonne[3], Karsten Kristiansen[3] and Nils J. Færgeman[1]

[1] Department of Biochemistry and Molecular Biology, University of Southern Denmark, DK-5230 Odense M, Denmark
[2] IGM-Bioorganic Chemistry, Faculty of Life Sciences, University of Copenhagen, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark
[3] Department of Biology, University of Copenhagen, Ole Maaløes Vej 5, 2200 København N, Denmark

Plants constitute a formidable reservoir of bioactive compounds, and throughout history plants and plant extracts have been used for treatment of various diseases. Around half of modern drugs have their origin in plants or microorganisms [1]. Apart from being sources of interesting lead compounds for drug discovery, plants also constitute an important food source, and it is well documented that intake of various types of plants and fruits has health beneficial effects and may prevent or ameliorate life style diseases such as obesity and obesity related dysmetabolic syndrome.

An organism's ability to regulate the production, storage and release of energy is vital for health and survival. A major source of energy is stored as lipids, however, abnormalities in fat accumulation produce pathological states, including obesity, increased risk of cardiovascular diseases, type II diabetes mellitus, and hypertension. The alarming worldwide increase in obesity has intensified the search to identify genes that control the development, differentiation, and function of fat-storing tissues. While some key regulators of these pathways were identified with biochemistry and cell culture systems, a number of invertebrate genetic model systems have accelerated the discovery of new genes important in fat biology. One such model is *Caenorhabditis elegans*, which recently was used to identify approximately 400 genes that affected lipid accumulation when knocked down by RNA interference (Ashrafi et al. 2003).

C. elegans is being increasingly recognized as the prototypical eukaryote which possesses all the essential metabolic pathways of higher (mammalian) organisms. Most of the structural genes have counterparts in mammalian systems that share 30% or more amino acid identity, indicative of structural and functional homology. Furthermore, gene knock outs are often available, and double mutants are easily made, making the genetic investigation of pathways fairly easy in *C. elegans*.

The study presented here shows some of the preliminary data on crude plant extracts as well as more extensive data on the effect of chemically modified isoflavonoids of soy bean origin. The fluorescent triacylglycerol-binding dye Nile red was used in a screening for TAG-content lowering compounds and based on this Nile red data the compound Cgt3-1,8 was selected for further investigation. This compound markedly reduces the Nile red staining without affecting worm physiology, and this is not mediated through *daf-2* (insulin signaling), *daf-7* (TGFβ-signaling), or *tph-1* (serotonin signaling). Furthermore it increases life span of the worm significantly which is not mediated through Sir-2, a histone deacetylase known to regulate chromatin packaging and gene expression and hence life span.

We are currently investigating whether the life span effect is due to signaling through AMPK (AMP activated protein kinase) and conducting analysis of changes in gene expression by RNA-array (Affymetrix) in an effort to identify cellular functions and metabolic pathways that are affected by the presence of Cgt3-1,8.

1. Newman D. J. and Cragg G. M. (2007) Natural Products as Sources of New Drugs over the Last 25 Years. Journal of Natural Products Vol. 70 (3), 461-477